115 (2638)

Studies to determine the biological significance of the vitamins.

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Earlier authors have fully appreciated that conditions other than food and oxygen are necessary for an active growth of cells in the body. This fact is well exemplified in the work of Morgan[1] on the regeneration of the legs of salamanders. Morgan noted that the legs of these animals regenerate as rapidly in starved as in well fed animals. I have sought these other conditions by means of the tissue culture, and find they are a *crowding of the cells* and *stagnation.* Single isolated cells or small groups of cells will not grow in a drop of plasma. For these cells to grow they must be crowded with other cells to form a compact mass of considerable size, and be placed in a small amount of stagnant medium so that the loss of soluble materials from the mass is reduced to a minimum. In the presence of oxygen the cells in such a mass begin to grow after a given latent period.[2]

In analyzing these factors of cell crowding, stagnation, oxygen and latent period more carefully, I have further found that they signify that growth depends on the accumulation of a certain concentration of an oxydative product of these cells. This product can be readily extracted with salt solution, and when added in a certain concentration to a drop of plasma it will stimulate growth in isolated cells placed in the mixture. In lower concentrations (S_2) it stimulates these cells to migrate and store proteins and fats. Only in certain high concentrations (S_3) can the cells digest these proteins and fats and grow. In all higher concentrations (S_4) it leads to the digestion of the protoplasm of the cells themselves. I have named this substance or substances the *archusia,* the driving substance of the cell.[3, 4] It corresponds to the heat in the steam engine. It cannot accumulate in any tissue

[1] Morgan, T. H., *Jour, Exp. Zool.*, 1906, iii, 457.

[2] Burrows, M. T., Trans. *Cong. Am. Phys. and Surgeons,* 1913, ix, 77.

[3] Burrows, M. T., *South. Med. Jour.*, 1924, xvii, 233.

[4] Burrows, M. T., PROC. SOC. EXP. BIOL. AND MED., 1923, xxi, 94.

having a rich and active blood supply unless the blood has become saturated with it from other sources.

Through the careful extraction of the various tissues of the body it has been found that the growth rate of these tissues corresponds to the amount of *archusia* contained within them. This concentration of the *archusia,* it being a normal product of the oxydative reaction of the cells, can be increased by crowding the cells and reducing the circulation to them, or it may be maintained from outside sources. Cancer I have shown to be nothing more than the result of a primary crowding of the cells together and a relative reduction in their blood supply. As the crowding and the stagnation reaches certain proportions, the mass acquires the property of independent growth. This mass continues to reproduce itself in that it preys upon and destroys surrounding tissues and blood vessels.[5]

The active growth in the bone marrow, nails, sex glands and in wounds is maintained by the same conditions of stagnation of circulation and cell crowding.[5] These factors are only less in degree than in cancer. In development the greatest growth is in early life. This growth wanes with the development of the blood vascular system and an active circulation. The embryonic tissue of the 5 day old chick-embryo differs from cancer only in that the number of cells per unit capillary area is greater in cancer or the blood supply is less. To transform an embryonic or adult fragment to cancer, it is necessary to stimulate a growth of cells outside the blood vessels (to increase the cells per unit capillary area), or reduce the number of capillaries in the fragment without disturbing the cells. Unchanged embryonic fragments when transplanted into a host form benign tumors; when the cells in them are increased proportionally over the blood vessels they become malignant tumors when transplanted to a host.[6]

By these observations and others on coal tar,[7, 5] etc., we have found the nature of the cancerous organization and the manner by which it is brought into existence. How the normal functioning organism is developed, and how it maintains its organization remained for solution. In comparing the amount of stagnation and cell crowding necessary for a growth of body cells, it was

[5] Burrows, M. T., *J. Med. Research,* 1924, xliv, 615.

[6] Burrows, M. T., *J. Mo. State Med. Assoc.,* 1923, xx, 145.

[7] Jorstad, L. H., PROC. SOC. EXP. BIOL. AND MED., 1923, xxi, 67.

noticed that most tissues, even those of the fœtus and the young child, are too richly supplied with blood for growth to intervene, unless their blood be supplied with growth stimulus from other sources. We have sought a source for this stimulus in the glands of internal secretion and in the food. Johnston and I[8] have studied by a new method the action of the ovary in this capacity. We have found that the Allen, Doisy hormone stimulates an active digestion of fat and an active growth of the subcutaneous connective tissue cells. Other authors have noted its action on the uterus, breasts and other sexual organs.

Edwin Smith in his work on the production of tumors by the *B. tumefaciens* showed that this organism stimulates an active growth of cells in the plant. Recently Blumenthal, Auler and Meyer[9] have isolated a similar organism from human cancers, and reproduced cancers in plants and animals. The action of this organism on the animal cells is quite identical to the extracts of any actively growing tissue from the animal as noted above. It became of interest to see what might be the action of this organism when fed to animals. Jorstad and I have fed two day old cultures of this organism as well as similar cultures of the *B. campestris,* an organism which produces a primary stimulation and then a destruction of plant cells. Chamber[10] while working here in the laboratory showed that the *B. campestris* destroys the plant cells through its ability to break up starch. This ability to split starches does not develop early but late in the cultural life of the organism.

For controls animals were fed:

Potato Starch	80 grams
Egg Albumin	50 "
McCollum Salt Mixture	10 "
Autolyzed Yeast (Vegex[11])	10 "
Butter	30 "

In the experiment 20 cc. of a 2 day old culture of the organism in a simple potato decoction were substitued for the yeast. In other experiments the butter was replaced by crisco to determine if the organism replaces vitamin B (yeast), vitamin A, or both.

In the accompanying curve 1, the results of one of these experiments are given. Both bacteria act in a diet with butter as active and normal growth stimuli. Growth fails when the butter

[8] Presented 1924, *Am. Soc. Exp. Path.*, Washington, D. C.

[9] Blumenthal, Auler and Meyer, *Zeitsch. fur Krebsforsch.*, 1924, xxi, 387.

[10] Article in Press.

is left out of the diet. These bacteria replace vitamin B, but contain no noticeable amount of vitamin A.[11]

As is noticed therefore, these organisms when placed outside the vessels or into the tissue, stimulate a densely cellular and non-vascular or cancerous organization. When transmitted inside the blood vessels where they act on the endothelial cells first they stimulate the growth of a normal vascular and functioning tissue.

In other papers on muscular contraction,[12] I have shown that function is the result of a polarization of the cell. This polarization is induced by the growth of blood vessels and the rate of circulation. This increased blood supply inhibits growth and utilizes the same energy for function. It is possible, as the above experiments indicate, that the body survives in that it has certain internally secreting glands adapted to liberate stimuli and in preying on lower growing and non-functioning forms. If this be true the higher function in animals must be purely the result of an evolutionary development. These higher types have not only developed their vascular organization and function, but survive because they can prey for a part of their life's energy on lower non-functioning forms, and have glands which liberate *archusia* into their circulating medium.

By these observations it has been possible to throw light not only on the nature of these formative mechanism of development and the evolution of function in higher animals, but also on the biological significance of vitamins, and to give further proof that cancer is nothing more than the result of an abnormal arrangement of cells. Normal development proceeds when a normal growth stimulus is transmitted through the blood stream where it acts to cause a primary development of blood vessels and secondary development of the tissues. Cancer develops when the same stimulus is placed outside the blood vessels or into the tissues so that the cells grow to form a densely cellular and non-vascular tissue. We have shown that coal tar acts in the same capacity, not by stimulating cells to proliferate and thus to form the non-vascular and cellular tissue, but by attracting cells from a wide area of the tissue and collecting them in dense masses about drops of it. Growth intervenes as these cellular masses become sufficiently large and stagnant.

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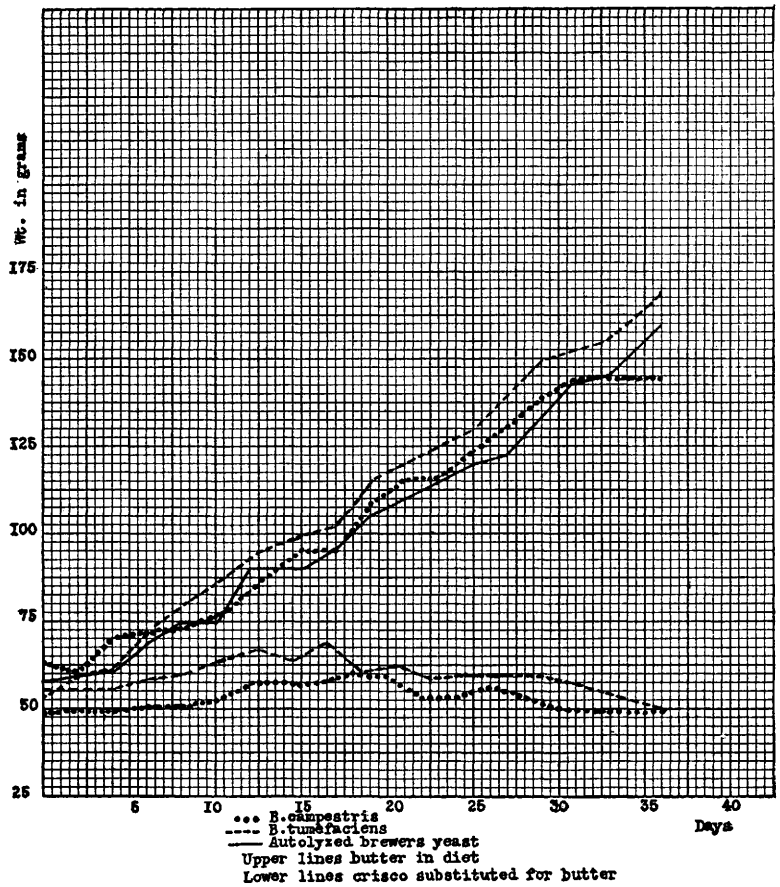
[11] Supplied by The Vitamin Food Co., Westfield, Mass.

[12] Burrows, M. T., *Am. J. Physiol.*, 1917-18, xlv, 556.



CURVE No. 1. The three upper lines show the growth of rats fed on a diet containing butter and respectively *B. campestris, B. tumefaciens* and vegex. The two lower lines show the growth of rats on a diet containing *B. tumefaciens* and *B. compestris* respectively, but no butter.